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(54) Hochdisperse pharmazeutische Zusammensetzung.

(57) Es wird eine hochdisperse pharmazeutische Zusammensetzung beschrieben, die als Mikroemulsion vorliegt und durch Mischen von mit Ionenpaarbildnern modifiziertem sauren oder basischen Wirkstoff, Isoproylmyristat als Fettkomponente, Polyoxyethylen-fettsäureester und/oder Polyoxyethylenalkoholether als Tensid, Polyoxyethylen-glycerinfettsäureester als Cotensid und Wasser erhältlich ist. Die Zusammensetzung weist hohe Wirkstoffkonzentrationen auf und ist insbesondere zur nasalen, rektalen und transdermalen Applikation geeignet.

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Europäisches Patentamt

EUROPÄISCHER RECHERCHENBERICHT

Nummer der Anmeldung

EP 90 10 4167

EINSCHLÄGIGE DOKUMENTE

Kategorie	Kennzeichnung des Dokuments mit Angabe, soweit erforderlich, der maßgeblichen Teile	Betrifft Anspruch	KLASSIFIKATION DER ANMELDUNG (Int. Cl.5)
Y	EP-A-0 152 945 (BERND W. W. MÜLLER) * Seite 7, Zeile 1 - Zeile 26 * * Seite 8, Zeile 18 - Zeile 26 * * Seite 9, Zeile 24 - Zeile 35 * * Seite 12, Zeile 11 - Seite 13, Zeile 29; Ansprüche 1-21 *	1-16	A61K9/107 A61K47/20 A61K47/18 A61K47/48
Y,D	EP-A-0 214 501 (AMERICAN CYANAMID COMPANY) * Seite 6, Zeile 32 - Seite 8, Zeile 20 * * Seite 17, Zeile 14 - Seite 19, Zeile 20; Ansprüche 1-15 *	1-7, 13-16	
Y	EP-A-0 189 861 (SHOWA DENKO K.K.) * Seite 5, Zeile 4 - Seite 10, Zeile 15 *	8-12	
A	PATENT ABSTRACTS OF JAPAN vol. 10, no. 239 (C-367)(2295) 19. August 1986 & JP-A-61 072 714 (TAIYO YAKUHIN KOGYO K.K.) 14. April 1986 * Zusammenfassung *	1-18	
A	EP-A-0 274 870 (T.I.L. MEDICAL LTD.) * Seite 7, Zeile 34 - Zeile 38; Ansprüche 1-11 *	1-18	

RECHERCHIERTE SACHGEBIETE (Int. Cl.5)
A61K

Der vorliegende Recherchenbericht wurde für alle Patentansprüche erstellt

Recherchenort	Abschlußdatum der Recherche	Prüfer
BERLIN	07 JULI 1992	SIATOU E.

KATEGORIE DER GENANNTEN DOKUMENTE

X : von besonderer Bedeutung allein betrachtet
Y : von besonderer Bedeutung in Verbindung mit einer anderen Veröffentlichung derselben Kategorie
A : technologischer Hintergrund
: nichtschriftliche Offenbarung
P : Zwischenliteratur

T : der Erfindung zugrunde liegende Theorien oder Grundsätze
E : älteres Patentdokument, das jedoch erst am oder nach dem Anmeldedatum veröffentlicht worden ist
D : in der Anmeldung angeführtes Dokument
L : aus andern Gründen angeführtes Dokument

& : Mitglied der gleichen Patentfamilie, übereinstimmendes Dokument

EPO FORM 1503 03.82 (P0403)

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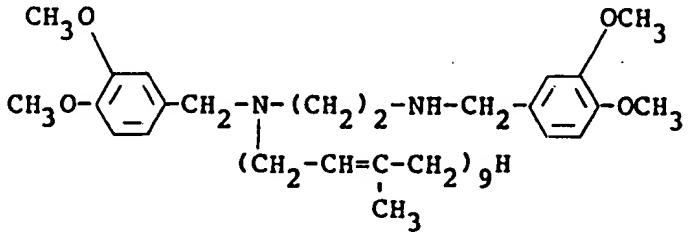
BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to a novel lipid emulsion having the activity of potentiating the anti-cancer activity of an anti-cancer agent, a method of potentiating the activities of anti-cancer agents by using it with the lipid emulsion, and to a method of treating cancer occurring in a warm-blooded animal by administering the novel lipid emulsion in combination with anti-cancer agents to the warm-blooded animal.

2. Description of the Prior Art

N-solanesyl-N,N'-bis(3,4-dimethoxybenzyl)ethylenediamine of the following formula (II)



is a known compound.

The compound of formula (II) is described in the patent literature as one of a series of isoprenylamine derivatives having antiviral and antitumoral activities (see, for example, Japanese Laid-Open Patent Publication No. 192339/1982 and its corresponding U. S. Patents Nos. US-A-4645862, US-A-4658063, US-A-4700002 and US-A-4723008).

In recent years various carcinostats and anti-cancer agents against solid tumors such as lung cancer, stomach cancer, breast cancer, bladder cancer and testicular tumor or tumors in the hematopoietic organs such as leukemia and malignant lymphoma have been developed, but no drug has yet come out which can completely cure or prevent these malignant tumors. For example, cyclophosphamide (CPA), melphalan (MPL), nimustine (ACNU), carboquone (CQ), vincristine (VCR), vinblastine (VLB), vindesine (VDS), bleomycin (BLM), 5-fluorouracil (5-FU), adriamycin (ADM), cisplatin (CDDP), actinomycin D (ACD), methotrexate (MTX), aclarubicin (ACR), toyomycin (TM), neocartinostatin (NCS), and ifosfamide (Ifos) have been used heretofore therapeutically as anti-cancer agents (the parenthesized letters show abbreviated designations) which may sometimes be used hereinafter). These drugs are used selectively and specifically in various areas because of their inherent anti-cancer spectra. For example, adriamycin (ADM) has a broader anti-cancer spectrum than other drugs, and is used against breast cancer, bladder cancer, lung cancer, testicular tumor, malignant lymphoma, and acute leukemia. However, the efficacy of ADM on these diseases is limited, and cancer cells showing resistance to ADM have appeared. A further cumbersome and complex problem is that other drugs do not show an anti-cancer action on these ADM-resistant cancer cells.

The appearance of drug-resistant tumor cells also becomes a problem with drugs other than ADM.

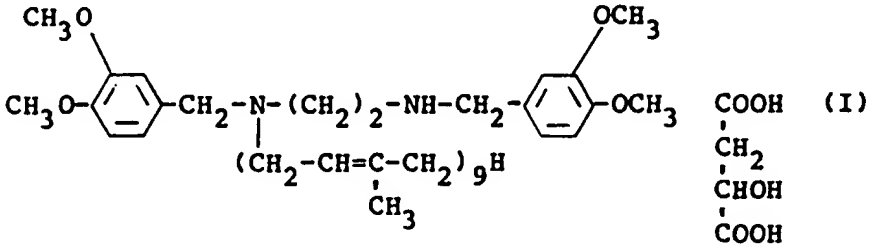
Recently, searching of compounds effective on these drug-resistant tumor cells was considered, and it has so far found that when N-solanesyl-N,N'-bis(3,4-dimethoxybenzyl)ethylenediamine itself or its hydrochloride is combined with ADM, the pharmacological efficacy of ADM can be potentiated, particularly against ADM-resistant tumor cells. This finding was applied for a patent (Japanese Laid-Open Patent Publication No. 200913/1986).

The present inventors further made investigations in order to overcome the problem of the drug-resistance of tumor cells, and determined that an acid salt, especially a malate, of N-solanesyl-N,N'-bis(3,4-dimethoxybenzyl)ethylenediamine of formula (II) above has excellent anti-cancer activity as compared with the compound (II) and it hydrochloride and can potentiate the pharmacological efficacy of not only adriamycin but also other anti-cancer agents, particularly the anti-cancer activity of these compounds on drug-resistant tumor cells, and that this activity has some degree of specificity.

The present inventors have further found that when the malate of compound (II) is administered in a form incorporated in lipid microspheres by applying the drug deliv ry system (DDS), th lipid microspheres are transferred selectively to tumor cells, and the incorporated malat xhibits its effect in situ, and that this offers an effective therapeutic method.

SUMMARY OF THE INVENTION

This invention relates to a lipid emulsion containing N-Solanesyl-N,N'-bis(3,4-dimethoxybenzyl)-ethylenediamine malate represented by the following formula (I)



(I)

More specifically, this invention relates to a lipid emulsion having the action of potentiating the activities of anti-cancer agents. By using the lipid emulsion in combination with anti-cancer agents, the activities of the anti-cancer agents can be potentiated.

According to this invention, there is provided a pharmaceutical oil-in-water type micro-emulsion having the action of potentiating the activities of anti-cancer agents, said emulsion comprising

fine particles of a vegetable oil or a triglyceride of a medium-chain fatty acid having 8 to 12 carbon atoms containing 0.1 to 10 % (w/v) of N-solanesyl-N,N'-bis(3,4-dimethoxybenzyl)ethylenediamine malate of formula (I) above,

an aqueous medium, and

0.05 to 25 % (w/v) of a physiologically acceptable phospholipid for dispersing said fine particles in said aqueous medium.

In a preferred embodiment, the vegetable oil is pharmaceutically acceptable soybean oil.

In another preferred embodiment, the physiologically acceptable phospholipid is a purified vegetable oil phospholipid, preferably purified soybean oil phospholipid.

Preferably, an isotonizing agent is added to the lipid emulsion of the invention. Examples of the isotonizing agent are glycerol, sugar alcohols, monosaccharides, disaccharides, and amino acids. Thus, in a further preferred embodiment, there is provided a micro-emulsion consisting essentially of

5 to 50 % (w/v) of fine particles of a vegetable oil or a triglyceride of a medium-chain fatty acid having 8 to 12 carbon atoms containing 0.1 to 10 % (w/v) of N-solanesyl-N,N'-bis(3,4-dimethoxybenzyl)-ethylenediamine malate,

0.05 to 25 % (w/v) of physiologically acceptable phospholipid,

an isotonizing agent selected from the group consisting of glycerol, sugar alcohols, monosaccharides, disaccharides and amino acids in an amount sufficient to isotonize the emulsion, and

water.

In still another preferred embodiment, there is provided a pharmaceutical oil-in-water micro-emulsion consisting essentially of

5 to 30 % (w/v) of fine particles of soybean oil having dissolved therein 0.3 to 3 % (w/v) of N-solanesyl-N,N'-bis(3,4-dimethoxybenzyl)ethylenediamine malate of formula (I),

0.5 to 25 % (w/v) of a purified soybean oil phospholipid, and

the remainder being water.

According to a second aspect, the present invention provides a method of potentiating the activities of anti-cancer agents by administering the anti-cancer agents in combination with the lipid emulsion of the invention.

According to a third aspect of the invention, there is provided a method of effectively treating cancer occurring in a warm-blooded animal, which comprises administering an anti-cancer agent in combination with the lipid emulsion of the invention to the animal.

In a preferred embodiment, the lipid emulsion of the invention is intravenously administered.